

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>6</sup> : <b>A61K 31/24</b>		<b>A1</b>	(11) International Publication Number: <b>WO 97/37652</b>
			(43) International Publication Date: 16 October 1997 (16.10.97)
(21) International Application Number: <b>PCT/US97/05860</b>		(81) Designated States: AU, CA, JP, US, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).	
(22) International Filing Date: 10 April 1997 (10.04.97)			
(30) Priority Data: 08/632,338 10 April 1996 (10.04.96) US		<b>Published</b> <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
(60) Parent Application or Grant (63) Related by Continuation US Not furnished (CIP) Filed on Not furnished			
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(54) Title: <b>METHODS OF PROVIDING NEUROPROTECTION</b>			
(57) Abstract  Novel methods are disclosed for treating asymptomatic, acute and chronic neurological disease and attenuating further neuronal cell death in neurological diseases, employing a glycine site antagonist at the NMDA (N-methyl-D-aspartate) complex, e.g., 2-phenyl-1,3-propanediol dicarbamate (felbamate).			

## METHODS OF PROVIDING NEUROPROTECTION

FIELD OF THE INVENTION

The present invention relates to pharmaceutical compositions which are antagonists at the glycine site on NMDA (N-methyl-D-aspartate) receptor complex, and to methods for the attenuation of acute or chronic neuronal damage in neurological disease ("neuroprotection").

BACKGROUND OF THE INVENTION

Certain references cited below, which published in 1996, after the filing of the priority document, are not believed to represent prior art to the invention disclosed in the priority document (U.S. Serial No. 08/632,338), but are provided in order to simplify the explanation of the invention discussed herein.

The major excitatory neurotransmitter in the central nervous system is L-glutamate. The amino acids glutamate and aspartate cause convulsive activity when applied to the cerebral cortex (Hayashi, T., Jpn. J. Physiol., 3:46-64, 1952). Classification of the excitatory receptors include the AMPA, kainate and NMDA receptors (Watkins, J.C. Ann. Rev. Pharmacol. Toxicol., 21:165-204, 1981).

Unique features of the NMDA receptor-channel complex include: a sensitivity to blockade by physiological concentrations of  $Mg^{++}$ , a high permeability to  $Ca^{++}$ , and a requirement for coactivation by glycine. Thus, glycine and glutamate binding sites are allosterically coupled at the NMDA receptor complex. (Kemp, J.A., Trends Pharmacol Sci., 14(1):20-5, 1993).

Excitatory amino acid receptors are divided into NMDA and non-NMDA (kainate and AMPA) subtypes (Monaghan, D.T., Annu. Rev. Pharmacol. Toxicol., 29, 365-402, 1989). The NMDA receptor complex is located on the neuronal cell surface and is comprised of multiple

agonist has been shown to increase the potency of NMDA in inducing seizures in mice (Singh, L., Eur. J. Pharmacol., 186:129-132, 1990).

Functional glycine antagonists can have either high intrinsic activity (D-cycloserine) or low intrinsic activity (HA-966). The compound HA-966 also displays weak partial agonist effects at the glycine site and bears the risk of proconvulsant activity (Wlaz, P., Eur. J. Neurosci, 6(11):1710-1719, 1994).

Felbamate (2-phenyl-1,3-propanediol dicarbamate) is a known pharmaceutical compound having been described in U.S. Pat. Nos. 2,884,444 (1959). Felbamate is a glycine site antagonist at the NMDA receptor.

U.S. patent 4,978,680 relates to the use of felbamate for the prevention and control of epileptic seizures. U.S. patent 5,082,861 relates to the use of felbamate for the prevention and control of epileptic seizures associated with complex partial seizures. U.S. patent 5,292,772 relates to the use of felbamate for the prevention and control of epileptic seizures associated with Lennox-Gastaut syndrome. U.S. patent 4,868,327 discloses a synthesis of felbamate.

Felbamate is a modulator of NMDA receptor function, and a glycine site antagonist (McCabe, R.T., J. Pharmacol. Exp. Ther., 264(3):1248-1252, 1993, Sofia, R.D., Ann. Neurol., 36(4):677-678, 1994, Wamsley, J.K., Exp. Neurol., 129(2):244-250, 1994, Taylor, L.A., Eur. J. Pharmacol., 289(2):229-233, 1995, White, H.S., Epilepsy Res., 20(1):41-48, 1995) but also has other reported mechanisms of actions (White, H.S., Epilepsia, 33(3):564-572, 1992, De Sarro, G., Eur. J. Pharmacol, 262(1-2):11-19, 1994, Serra, M., Eur. J. Pharmacol, 265(3):185-188, 1994, Rho, J.M., Ann. Neurol., 25:229-234, 1994, Subramanian, S., J. Pharmacol. Exp. Ther., 273:878-886, 1995). Felbamate does not cause the transient neuropathological changes seen in brain neurons after competitive antagonist administration (Olney, J.W., Arch. Gen. Psych., 52:998-1007, 1995).

(Kanthasamy, A.G., Brain Res 705:97-104, 1995), or glycine site antagonist mechanism of action (Rho, J.M., Ann. Neurol., 25:229-234, 1994, Subramanian, S., J. Pharmacol. Exp. Ther., 273:878-886, 1995).

In culture, antagonism of the glycine site or channel of the NMDA receptor prevents hypoxia-induced degeneration (Priestly, T., Brain Res., 531:183-8, 1990). In animal models of stroke (ischemia), felbamate was found to decrease neuronal death and delayed-ischemic necrosis when administered post-hoc (Wasterlain, C.G., Neurology, 43:2303-2310, 1993) and delayed apoptosis of the CA1 hippocampal granule cells (Wasterlain, C.G., Stroke, 27:1236-1240, 1996). Felbamate has been proposed as a therapeutic treatment for the prophylaxis of stroke in humans (Fisher, M., Stroke, 25(5):1075-1080, 1994).

Excessive NMDA receptor activation by excitatory amino acids or neurotoxic mediators of inflammation has been implicated in the pathogenesis of acute and chronic neurological diseases (Beal, M.F., FASEB J. 6:3338-3344, 1992). In acute neurological disorders, a sudden toxic elevation of glutamate may cause neuronal death by overstimulation of the NMDA receptor. In chronic neurological disease, defective mitochondrial function or abnormal cellular metabolism may result in excitotoxic death by increasing the vulnerability of the neuronal cells to endogenous glutamate (Novelli, A., Brain Res., 451:205-212, 1988, Simpson, J.R., Exper. Neurol., 121:57-64, 1993, Henneberry, R.L., Ann. NY. Acad. Sci., 568:225-233, 1989). Bioenergetic defects resulting in cellular energy depletion would produce resting membrane depolarization and a subsequent removal of the Mg++ dependent NMDA receptor block. These events would produce neuronal susceptibility to normally non-toxic effects of endogenous glutamate resulting in accumulation of intracellular calcium and delayed neuronal death (Cox, J.A., Brain Res., 499:267-272, 1989, Beal, M.F., Ann. Neurol., 31:119-130, 1992). Abnormal NMDA receptors

hepatic failure in 11 patients with 4 deaths (O'Neil, M.G., Neurology, 46:1457-1459, 1996). As a result, the FDA and the manufacturer sent a letter to all physicians in August 1994 requiring the withdrawal of felbamate from patients except in those cases in which the risk of seizure exceeded the risk of aplastic anemia. Warnings were added to the prescribing information and a blood test was required every two weeks. In a study published after the FDA warning (Li, L.M., Eur. Neurol., 36:146-148, 1996) one-hundred and eleven patients with refractory epilepsy were treated with adjunctive felbamate therapy. No cases of aplastic anemia or hepatic failure were observed when serum levels of anti-convulsant drugs were monitored. In addition, the safety of felbamate in a suicidal overdose was reported (Nagel, T.R., Ped. Emerg. Care., 11(6):369-371, 1995). An adolescent patient acutely consumed a total oral dose of 6900 mg and suffered no neurological, hematological or hepatic abnormalities.

Other reported adverse events include thrombocytopenia (Ney, G.C., Neurology, 44:980-981, 1994), toxic epidermal necrolysis (Travagline, M.T., Pharmacotherapy, 15(2):260-4, 1995) anaphylaxis (O'Neil, M.G., Ann. Pharmacother., 29(4):430, 1995) mania (Hill, R.R., Psychosomatics, 36(4):404-6, 1995) psychosis (Knable, M.B., J. Clin. Psychopharmacol., 15(4):292-3, 1995) and movement disorder (Kerrick, J.M., Neurology, 45(1):185-7 1995).

#### OBJECTS OF THE INVENTION

One of the objects of the present invention is to provide compositions and methods for the treatment of acute and chronic neurological disorders that involve excessive activation of the NMDA receptor.

Another object of the present invention is to provide a method for attenuation of cell death caused by excessive activation

drug is given prophylactically and chronically when the patient has asymptomatic or pre-clinical neurological disease.

The invention also relates to a method of determining NMDA receptor level in a mammal comprising administering labeled felbamate, and determining the amount of labelled felbamate which is bound to neurons.

#### DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to pharmaceutical compositions and to methods for the attenuation of acute and chronic neurological disorders that involve excessive activation of the NMDA receptor. Advantageously, the present invention relates to methods for neuroprotection in neurological disease(s) through the administration of therapeutic compositions, either intravenously or orally, which contain for example, as an active ingredient 2-phenyl-1,3-propanediol dicarbamate, commonly known as felbamate. The compound felbamate may be administered prophylactically, acutely, subacutely or chronically, depending on the various neurological disease states. This compound has multiple mechanisms of action, of which one is a glycine site antagonist at the NMDA (N-methyl-D-aspartate) receptor.

NMDA receptor antagonists can be divided into noncompetitive (acting at the receptor channel complex) and competitive (acting at the NMDA recognition site) or modulatory sites (glycine, polyamine).

Although a competitive channel blocker can reduce damaging overstimulation of the excitatory portion of the receptor, it is also likely to eliminate the receptor's normal physiological functions. Thus, cognitive and memory brain functions are compromised and hence, most channel blockers cannot be administered safely to humans. In contrast, antagonists of receptor modulatory sites inhibit the toxic effects of high glutamate concentrations while sparing physiologic

to their clinical expression when neuronal cell death has already significantly occurred (Albin, R.L., NEJM 322:1293-1298, 1990). In a variety of neurological diseases, symptoms do not occur until levels of NMDA receptors are greatly reduced. Diseases where this diagnostic technique is particularly useful include Parkinson's, Huntington's, Alzheimer's, Tourette's, adrenoleukodystrophy, CNS vasculitis, mitochondrial myopathies, HIV dementia, depression, ALS, movement disorders and Down's Syndrome.

#### THERAPEUTIC USES OF THE COMPOUNDS OF THE INVENTION

Felbamate and other antagonist at the glycine site of the NMDA receptor are useful in the treatment of multiple neurologic diseases, in which inflammatory neurotoxins and excitatory amino acids, of which at least glutamate is involved in the pathophysiology. ACEA compounds are administered at daily doses between 1-150 mg/kg, most advantageously between 20-40 mg/kg in each of the disorders discussed below.

#### **Prevention of Neuronal Degeneration and Brain Atrophy in Epilepsy**

Epilepsy, a disease which has been characterized as a paroxysmal, self-sustaining and self-limited cerebral dysrhythmia, genetic or acquired in origin and physiologic or organic in mechanism. Seizures which are evoked in an otherwise healthy brain by other factors (alcohol withdrawal, metabolic conditions, cocaine, etc.) are termed non-epileptic seizures. Epilepsy is usually classified, by clinical and electro-encephalographic observations, into four general classes:

- 1) Grand mal
- 2) Petit mal

There is considerable controversy as to whether epileptic activity is a cause or consequence of the neuronal damage (i.e., gliosis, atrophy, decrease number of dendritic spines) observed in brain tissue (Thompson, S.M., Brain Pathol., 3:413-419, 1993). It has been proposed that the excitotoxic effect of elevated levels of glutamate and aspartate prior to seizures are insufficient to cause neuronal loss (Meldrum, B.S., Brain Pathol., 3:405-412, 1993). In addition, it is not currently thought that neuronal loss accompanies brief individual seizures since no quantitative data from animal experiments show that a single brief seizure (less than five minutes duration) can cause neuronal cell loss (Meldrum, B.S., Brain Pathol., 3:405-412, 1993).

Glycine site antagonists have been shown to act as anticonvulsant agents (Croucher, M.J., Neurosci. Lett., 118:29-32, 1990, Croucher, M.J., Brain Res., 543:91-96, 1991) although glycine antagonists with low intrinsic efficacy have proconvulsant activity (Wlaz, P., Eur. J. Neurosci., 6(11):1710-1719, 1994). In convulsant-treated cultures, non-competitive NMDA antagonists were unable to reduce cell death (Thompson, S.M., Brain Pathology, 3:413-419, 1993).

In a study of the etiology of complex partial seizures using microdialysis, elevated levels of glutamate occur prior to a complex partial seizure in humans (During, M.J., Lancet, 341:1607-1610, 1993). In addition, resting levels of glutamate were elevated in the temporal lobes in one-third of these patients.

We propose a novel hypothesis that congenital or environmental abnormalities produce alterations in glutamate metabolism and other amino acid metabolism. Both elevated resting glutamate levels and pre- and post epileptic elevations of glutamate cause acute but more commonly a chronic over-stimulation of the NMDA receptor. Prolonged chronic exposure may eventually cause metabolic or quantitative and qualitative abnormalities of the NMDA receptor resulting in delayed



regimens as polytherapy. There is currently no recognized serum therapeutic range for felbamate. Due to drug interaction, this results in substantially lower serum felbamate levels in patients. In addition, although felbamate monotherapy has resulted in several isolated reports of serum levels greater than 100 µg/ml, no patient has been on felbamate monotherapy for at least one year, or sustained a serum level greater than 100 µg/ml for at least one year. We propose that serum felbamate levels of at least 100 µg/ml for a duration greater than one year is necessary for neuroprotection against both chronically elevated brain glutamate levels and acute, episodically elevated pre- and post-seizure glutamate levels.

Felbamate, administered chronically in oral doses of 100-15,000 mg/day, advantageously 1200-7200 mg/day (serum levels ranging from 25-300 µg/ml), is efficacious in attenuating neuronal cell death from acute elevations of glutamate during seizures. More advantageously, serum levels ranging from 100-300 µg/ml, is efficacious in preventing delayed cell death, apoptosis, and atrophy in epilepsy when administered chronically for at least one year in duration.

### **Sepsis**

In systemic blood infections, coma and cardiac/respiratory dysfunction can lead to death. Coma and neurological dysfunction occur after the administration of antibiotics, which are believed to increase the release of toxins as they kill bacteria. Elevated levels of quinolinic acid cause neuronal death by NMDA receptor over-stimulation. Toxins from the bacteria are believed to increase the production of cytokines and CSF-quinolinic acid (Heyes, M., Brain, 116:1425-1450, 1993) causing neurological symptoms and neuronal cell death by NMDA receptor over-stimulation.

disorder, suggesting that cytokines and quinolinic acid are involved in its etiology. A glycine site NMDA antagonist has efficacy as an anticonvulsant as well as a neuroprotectant.

Felbamate, administered chronically in oral doses of 100-15,000 mg/day, advantageously 1200-7200 mg/day (serum levels ranging from 25 µg - 300 µg/ml), is efficacious in preventing neuronal death and seizures in ADL.

#### **CNS Vasculitis**

CNS vasculitis, an inflammatory condition of the cerebral arteries, occurs in multiple autoimmune diseases (i.e., rheumatoid arthritis). Neurological sequela include stroke, seizures and dementia. Quinolinic acid has been found to be elevated and correlate with the degree of brain damage by MRI and clinical dementia.

A glycine site NMDA antagonist has efficacy in preventing the neurological the sequela of CNS vasculitis (stroke, seizure and dementia). Felbamate, administered chronically in oral doses ranging from 100-15,000 mg/day, advantageously 1200-7200 mg/day (serum levels ranging from 25 µg - 300 µg/ml), is efficacious in preventing neuronal degeneration in CNS vasculitis.

#### **Impotence**

Penile erection is induced by the NMDA receptor activation of nitric oxide in the paraventricular nucleus of the hypothalamus (Melis, M.R., Neuro. Sci. Lett., 179:9-12, 1994). Epilepsy patients treated with felbamate, an antagonist at the glycine site of the NMDA receptor complex, reported an increase in libido. A common side effect of felbamate is increased mental energy and alertness.

A glycine site NMDA antagonist decreases primary and secondary impotence. Felbamate, administered chronically in oral

µg - 300 µg/ml), is efficacious in preventing neuronal degeneration and brain atrophy in schizophrenia.

#### Drug Addiction

Symptoms of opiate withdrawal in drug addiction may be in part mediated by the NMDA receptor complex in the rostral medulla. Felbamate has been reported to attenuate the severity of naloxone precipitated withdrawal in a dose related manner in rats (Kosten, T.A., Neuropsychopharm., 13:323-333, 1995). A glycine site antagonist at the NMDA receptor with properties of oral or IV administration, good tolerability, and low adverse experience profile is a treatment for drug addiction, tolerance, dependency and withdrawal.

Felbamate can be administered most advantageously by the intravenous route or chronically in oral doses at the time of diagnosis of withdrawal symptoms and chronically in oral doses for six months or more after recovery. Felbamate, administered chronically in oral doses ranging from 100-15,000 mg/day, advantageously 1200-7200 mg/day (serum levels ranging from 25 µg - 300 µg/ml), is efficacious in preventing the autonomic and mental adverse experiences of drug addiction.

#### Multiple Sclerosis

A portion of the cortical brain damage that occurs in acute attack of multiple sclerosis (MS) and chronic progressive MS is due to an inflammatory upregulation of cytokines and quinolinic acid (Heyes, M., Brain, 116:1425-1450, 1993). Brain atrophy and cognitive dysfunction are common in MS.

A glycine site NMDA antagonist has efficacy in protecting cortical neurons ("neuroprotection") in MS. Felbamate, administered chronically in oral doses ranging from 100-15,000 mg/day,

µg - 300 µg/ml), is efficacious in preventing neuronal degeneration from lead poisoning.

#### Mitochondrial Dysfunction

Mitochondrial dysfunctions are characterized by a mitochondrial abnormality (intracellular structures which produce energy for the cells) and other inherited or acquired biochemical disorders (Beal, M.F, Ann. Neurol. 31:119-130, 1992). Diseases or conditions include MELAS syndrome, MERF syndrome, Leber's disease, Wernicke's encephalopathy, Rett syndrome, homocystinuria, hyperprolinemia, nonketotic hyperglycinemia, hydroxybutyric aminoaciduria, sulfite oxidase deficiency, and combined systems disease (B12 deficiency).

A glycine site NMDA antagonist provides neuronal protection in these conditions. Felbamate can be administered most advantageously by the intravenous route or chronically in oral doses at the time of diagnosis and chronically in oral doses for six months or more after recovery. Felbamate, administered chronically in oral doses ranging from 100-15,000 mg/day, advantageously 1200-7200 mg/day (serum levels ranging from 25 µg - 300 µg/ml), is efficacious preventing neuronal degeneration in mitochondrial myopathies.

#### HIV Dementia

Patients who become HIV(+) have early pre-clinical brain neuronal deterioration as measured by NMR spectroscopy. When HIV(+) patients convert to AIDS, brain involvement produces dementia and is universally fatal. The mechanisms of brain deterioration appear to involve production of neurotoxic substances (i.e., quinolinic acid) that activate NMDA receptors and cause neuronal death by inducing intra cellular Ca<sup>++</sup> overload (Giulian, D., Science 250:1593-1596, 1990, Heyes, M.P., Ann. Neurol., 29:202-209, 1991a).

### Depression

Felbamate, a glycine site antagonist improves cognitive function and mood when administered to epileptic patients. Vegetative depression is characterized by low mood, excessive somnolence and obesity. Vegetative depression responds to a glycine antagonist by increasing mood, having a stimulatory effect and producing weight loss by NMDA mechanisms (Ketter, T.A., Epilepsy Res., 23(2):129-137, 1996). In addition, activation of the NMDA receptor, which are partly located on the serotonergic nerve terminal, elicits a release of cortical serotonin (Fink, K., Naumyn Schmiedebergs Arch. Pharmacol., 352(4):394-401, 1995) a major neurotransmitter in depression.

Felbamate, administered chronically in oral doses ranging from 100-15,000 mg/day, advantageously 1200-7200 mg/day (serum levels ranging from 25 µg - 300 µg/ml), is efficacious in treating vegetative depression.

### Amyotrophic Lateral Sclerosis

Amyotrophic Lateral Sclerosis (ALS) is a progressive disease of the motor tracts of the brainstem and spinal cord which produces muscle weakness, wasting and death. Excessive glutamate stimulation may be involved in the pathogenesis of this disease (Rothstein, J.D., Ann. Neurol., 28:18-25, 1990). The number of NMDA receptors in the spinal cord is reduced in patients with ALS (Shaw, P.J., Brain Res., 637:297-302, 1994). Abnormal glycine and glutamate metabolism produce neurotoxicity by NMDA mechanisms (Virgo, L., Brain Res., 676:196-204, 1995).

A glycine site antagonist, which prevents these NMDA receptors from being excessively stimulated, prevents weakness and death in ALS. Felbamate, administered chronically in oral doses ranging from 100-15,000 mg/day, advantageously 1200-7200 mg/day

15,000 mg/day, advantageously 1200-7200 mg/day (serum levels ranging from 25 µg - 300 µg/ml), is efficacious in treating ADD.

#### Narcolepsy

Narcolepsy is a sleep disorder in which patients have an acute onset of REM (dreaming) sleep. A glycine site NMDA antagonist has properties of cognitive enhancement and mental stimulation.

A glycine site NMDA antagonist is a useful treatment for narcolepsy. Felbamate, administered chronically in oral doses ranging from 100-15,000 mg/day, advantageously 1200-7200 mg/day (serum levels ranging from 25 µg - 300 µg/ml), is efficacious in treating narcolepsy.

#### Alzheimer's Disease

Alzheimer's Disease (DAT) is a progressive dementing illness which is caused by an abnormal form of amyloid deposition in the brain. Excessive amyloid deposition induces glutamate toxicity of the NMDA receptor (Koh, J-Y. Brain Res., 533:315-320, 1990, Mattson, M.P., J. of Neurosci., 12:376-388, 1992), resulting in neuronal death in areas of the brain that have a high density of NMDA receptors such as the hippocampus and cerebral cortex (areas of maximal neuronal death in DAT). The decrease in binding of NMDA receptors in DAT visual cortex correlated with increased numbers of neurofibrillary tangles. (Carlson, M.D., Neurobiol. Aging, 14(4): 343-352, 1993). Studies in animals have shown that glycine antagonist improve learning and attenuate scopolamine memory deficits (Fishkin, R.J., Behav. Neurol. Biol., 59(2):150-157, 1993, Finkelstein, J.E., Pharmacol. Biochem. Behav., 49(3):707-710, 1994, Baxter, M.G., Neurobiol. Aging, 15(2):207-213, 1994).

A glycine site NMDA antagonist with cognitive enhancement and neuronal protection properties is a useful treatment for DAT.

A glycine site NMDA antagonist with neuronal protection properties is a useful prophylactic treatment in all anesthetized patients. Felbamate can be administered most advantageously intravenously or orally within minutes to 24 hours of surgery and chronically in oral doses for six months or more. Felbamate, administered chronically in oral doses ranging from 100-15,000 mg/day, advantageously 1200-7200 mg/day (serum levels ranging from 25 µg - 300 µg/ml), is efficacious in preventing neuronal damage during surgical anesthesia.

#### **Traumatic Head and Spinal Cord Injury**

In the rat SDH (acute subdural hematoma) model, both pre- and post treatment with a glycine site antagonist significantly reduced hemispheric ischemic damage (Tsuchida, E., J. Neurotrauma, 12(3):279-288, 1995). The role of NMDA receptors has been implicated in the etiology of traumatic brain injury (Faden, A.I., Science, 244:798-800, 1989) and contusive spinal cord injury (Wrathall, J.R., Brain Res., 586:140-143, 1992). Felbamate was shown to have a neuroprotective effect against CA1 hippocampal neurons in an animal model of traumatic head injury (Wallis, R.A., Eur. J. Pharmacol., 294:475-482, 1995). Patients with head and spinal cord injury have been found to have elevated cerebrospinal fluid levels of quinolinic acid which implicates the NMDA receptor in the etiology of neuronal cell death.

A glycine site NMDA antagonist with neuronal protection properties is a useful prophylactic treatment in all head and spinal cord injured patients by protecting against hypoxia and glutamate stimulation of the NMDA receptor. Felbamate can be administered most advantageously intravenously or orally within minutes of the diagnosis of traumatic brain or spinal cord injury and chronically in oral doses for six months or more. Felbamate, administered

mg/day, advantageously 1200-7200 mg/day (serum levels ranging from 25 µg - 300 µg/ml), is efficacious in preventing neuronal death in Tourette's Syndrome.

#### **Hepatic Encephalopathy**

Hepatic encephalopathy is characterized by severe liver disease producing secondary neurological symptoms including seizures, cognitive dysfunction and extrapyramidal movements. NMDA receptors are involved in producing the latter three symptoms.

A glycine site NMDA antagonist with neuronal protection properties is a useful prophylactic treatment in all hepatic failure patients. Felbamate, administered chronically in oral doses ranging from 100-15,000 mg/day, advantageously 1200-7200 mg/day (serum levels ranging from 25 µg - 300 µg/ml), is efficacious in preventing neuronal death in treating seizures and neuronal degeneration in hepatic encephalopathy.

#### **Movement Disorders**

NMDA receptors are located in the subcortical areas of the brain which are involved in motor control. In a mouse model of posthypoxic myoclonus (a condition of hyperexcitability of the central nervous system), felbamate was found to have antimyoclonic properties. Felbamate has shown efficacy in control of tremor (Edwards, K.R., Neurology, 45:1951, 1995) and hemifacial spasm (Mellick, G.A., J. Pain and Symptom Management, 10:392-395, 1995) in humans at doses between 1800-2800 mg/day.

A glycine site antagonist is useful in the treatment of all movement disorders. Felbamate, administered chronically in oral doses ranging from 100-15,000 mg/day, advantageously 1200-7200 mg/day (serum levels ranging from 25 µg - 300 µg/ml), is efficacious in



mg/day (serum levels ranging from 25 µg - 300 µg/ml), is efficacious in preventing neuronal degeneration in Down's Syndrome.

#### **Electroshock Therapy (ECT)**

Patients who undergo ECT may suffer cognitive complications including memory loss. Since ECT is an artificially induced seizure, neuronal damage is similar to that of chronic seizures. A mechanism of cognitive dysfunction is damage to the NMDA receptors of the hippocampus and cerebral cortex. ECT has been shown to increase the turnover of NMDA receptors in animals.

A glycine antagonist such as felbamate prevents NMDA induced neuronal damage from ECT treatment. Felbamate is administered most advantageously intravenously or orally prior to the administration of ECT and chronically in oral doses for six months or more. Felbamate, administered chronically in oral doses ranging from 100-15,000 mg/day, advantageously 1200-7200 mg/day (serum levels ranging from 25 µg - 300 µg/ml), is efficacious in preventing neuronal damage and delayed cellular necrosis as a consequence of ECT therapy.

#### **Brain Tumors**

Brain tumors produce elevated levels of quinolinic acid (Heyes, M., J. Neurol. Sci., 133:112-118,1995) which produce seizures, neuronal degeneration and brain atrophy.

A glycine site antagonist such as felbamate, administered chronically in oral doses of 100-15,000 mg/day, advantageously 1200-7200 mg/day (serum levels ranging from 25 µg - 300 µg/ml), is efficacious in preventing seizures, neuronal degeneration and brain atrophy from brain tumors.

#### **Cerebellar Degeneration**

WHAT IS CLAIMED IS:

1. A method of protecting neuronal cells in a mammal having an acute or chronic neurological condition comprising administering a neuronal cell protecting amount of an antagonist of the glycine site of the NMDA receptor complex, to said mammal.

2. A method as in claim 1 wherein said chronic neurological condition is selected from the group consisting of: epilepsy, ADL, CNS vasculitis, impotence, schizophrenia, MS, fatigue, chronic lead poisoning, mitochondrial myopathies, HIV dementia, pain, depression, ALS, ADD, Parkinson's Disease, narcolepsy, Alzheimer's disease, drug addiction, Tourette's Syndrome, hepatic encephalopathy, movement disorders, Down's Syndrome, brain tumors and cerebellar degeneration.

3. A method as in claim 1 wherein said acute neurological condition is selected from the group consisting of: sepsis, meningitis, acute lead poisoning, hypoglycemia, childbirth, surgical anesthesia, and ECT.

4. A method as in claim 1 wherein said antagonist is selected from the group consisting of felbamate, quinoxalinediones including ACEA compounds (1011, 1021, 1031, 1328), pyridazinoindole, ACPC (1-aminocyclopropane carboxylic acid), 1,4 dihydroquinoxaline-2,3-diones, 4-hydroxy-2-quinolones, 4-amino-2-carboxytetrahydroquinolines and trans-4-hydroxy-pipecolic acid-4-sulfate.

5. A method as in claim 1 wherein said antagonist is felbamate.

6. A method as in claim 1 wherein said felbamate is administered intravenously.

7. A method as in claim 1 wherein said felbamate is administered orally or rectally.

8. A method for attenuation of cell death caused by excessive activation of the NMDA receptor by administering the drug

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US97/05860

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61K 31/24

US CL : 514/534

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/534, 541

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, CAS ONLINE

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4,978,680 A ( SOFIA ) 18 December 1990, claim 1.	1, 2, 4-8
X	US 5,292,772 A ( SOFIA ) 08 March 1994, claim 1	1, 2, 4-8
Y	CARTER, A. J. Glycine antagonists : regulation of the NMDA receptor-channel complex by the strychnine-insensitive glycine site.DRUGS OF THE FUTURE. 1992, Vol. 17, No.7, pages 595-613, especially pages 605-607.	1-8
Y	LEESON, P. D.et al. The glycine site on the NMDA receptor: Structure-activity relationships and therapeutic potential. 25 November 1994, Vol. 37, No.24. especially pages 4060-4061.	1-8

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance		
"E" earlier document published on or after the international filing date	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubt on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O" document referring to an oral disclosure, use, exhibition or other means		
"P" document published prior to the international filing date but later than the priority date claimed	"Z"	document member of the same patent family

Date of the actual completion of the international search

24 JUNE 1997

Date of mailing of the international search report

11 AUG 1997

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## INTERNATIONAL SEARCH REPORT

International application No. ✓  
PCT/US97/05860

### BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

Group I, claims 1-8, drawn to a method of treating an acute or chronic neurological condition, classifiable in class 514, subclass 534.

Group II, claims 9-11, drawn to a method of determining NMDA receptor levels, classifiable in class 560, subclass 164.

The inventions listed as Groups I and II do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The inventions listed as groups I and II are a combination of different categories of claims; see PCT Administrative Instructions Annex B Part I (c).

**PCT**WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau

## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup> :</b> <b>A61K 31/24</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 97/37652</b> <b>(43) International Publication Date:</b> 16 October 1997 (16.10.97)
<b>(21) International Application Number:</b> PCT/US97/05860 <b>(22) International Filing Date:</b> 10 April 1997 (10.04.97) <b>(30) Priority Data:</b> 08/632,338 10 April 1996 (10.04.96) US <b>(60) Parent Application or Grant</b> <b>(63) Related by Continuation</b> US Not furnished (CIP) Filed on Not furnished <b>(71)(72) Applicant and Inventor:</b> KOZACHUK, Walter, E. [US/US]; 8484 16th Street #300, Silver Spring, MD 20910 (US). <b>(74) Agents:</b> RHOA, Joseph, A. et al.; Myers, Liniak & Berenato, 6550 Rock Spring Drive # 240, Bethesda, MD 20817-1132 (US).	<b>(81) Designated States:</b> AU, CA, JP, US, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). <b>Published</b> <i>With international search report.</i> <i>With amended claims and statement.</i> <b>Date of publication of the amended claims and statement:</b> 13 November 1997 (13.11.97)	
<b>(54) Title:</b> METHODS OF PROVIDING NEUROPROTECTION <b>(57) Abstract</b> <p>Novel methods are disclosed for treating asymptomatic, acute and chronic neurological disease and attenuating further neuronal cell death in neurological diseases, employing a glycine site antagonist at the NMDA (N-methyl-D-aspartate) complex, e.g., 2-phenyl-1,3-propanediol dicarbamate (felbamate).</p>		

## AMENDED CLAIMS

[received by the International Bureau on 8 October 1997 (08.10.97);  
original claims 1-11 replaced by new claims 1-4 (2 pages)]

1           1. A method of treating sepsis and preventing  
2 neuronal degeneration and cell death in a human having  
3 sepsis, the method comprising the steps of:  
4           administering to the human having sepsis a  
5 neuronal cell protecting antagonist of the glycine site of  
6 the NMDA receptor complex, wherein said antagonist is 2-  
7 phenyl-1,3-propandeol dicarbamate at a serum level ranging  
8 from 25-300 ug/ml, in order to significantly attenuate  
9 neurological morbidity by preventing excessive stimulation  
10 of the NDMA receptor.

1           2. A method of treating HIV dementia and preventing  
2 neuronal degeneration comprising the steps of:  
3           administering to a human having HIV dementia a  
4 neuronal cell protecting antagonist of the glycine site of  
5 the NDMA receptor complex, said antagonist being 2-phenyl-  
6 1,3-propoandeol dicarbamate at a serum level ranging from  
7 25-300 ug/ml, in order to attenuate neurological morbidity  
8 by preventing excessive stimulation of the NMDA receptor in  
9 the human having HIV dementia.

1           3. A method of treating meningitis comprising the  
2 steps of:  
3           chronically administering to a human having  
4 meningitis a neuronal cell antagonist of the glycine site of

**STATEMENT UNDER ARTICLE 19**

This Amendment is submitted in order to bring the claims in the international application into conformity with those that have been allowed in the corresponding United States application. New claims 1-4 replaces all claims previously submitted.

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